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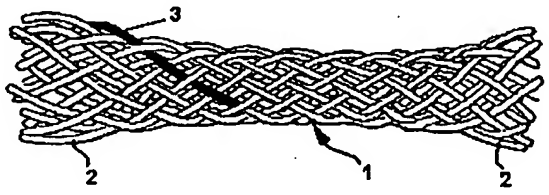

(57) Abstract

Polymeric compositions and devices for reducing or inhibiting the undesired effects or activity of matrix metalloproteinases (MMPs) in the body. Suitable devices include stents, catheters, guidewires, implants, or similar devices having a polymeric coating capable of inhibiting or countering the activity or effects of matrix metalloproteinases throughout the body. The compositions may further include one or more pharmaceutical agent.

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INHIBITION OF MATRIX METALLOPROTEINASES WITH POLYMERS AND PHARMACEUTICAL APPLICATIONS THEREOF

Field of the Invention

This invention relates to the use of polymer compositions as matrix metalloproteinase inhibitors.

Background of the Invention

Matrix metalloproteinases (MMPs) are metal-binding proteinases secreted by connective tissue cells, inflammatory phagocytes and transformed cells. The general structure of MMPs is centered around a zinc-containing catalytic domain. MMP activation requires dissociation of the zinc-cysteine interaction through proteolytic cleavage of the propeptide sequence or changes in the cysteine switch conformation by chemical perturbations. Proteolytic activation of pro-MMPs has been demonstrated by serine proteases such as tryptase, and chymase. Trypsin, chymotrypsin, plasmin, plasma kallikren, thermolysin, and urokinase also generate active MMPs *in vitro*.

Excessive activity of these enzymes has been associated with a variety of tumors including colorectal, cervical, lung, breast, bladder, prostate, skin cancers, and brain tumors. MMPs have been also been implicated in heart disease, impaired wound healing, and disruption of atherosclerotic plaques.

The degradation of extracellular matrix (ECM) components is a normal process associated with growth, morphogenesis, developments, remodeling and wound healing *in vivo*. MMPs are responsible for the degradation of ECM and basement membrane macromolecules. However, ECM and basement membrane destruction in excess has been found to contribute to the pathogenesis of many diseases.

Certain MMPs have been associated with vascular remodeling. These are the collagenases (including MMP-1), the stromelysins (such as MMP-3), the

gelatinases (including MMP-9 and MMP-2), and the membrane-type MMPs (MT-MMP). For example, injury to blood vessel walls has been linked with the expression of MMP-2 and MMP-9. MMP-2 is required for the migration of cultured vascular smooth muscle cells across complex extracellular matrix barriers and is critical in the formation of neointima. Expression of matrix metalloproteinases (MMP-2 and MMP-9) is upregulated by MT-MMP-1 following vascular injury.

Coatings for stents has become an intense area of research. Preferred metals for stents include Nitinol (currently preferred), stainless steel, and tantalum. Current coating technology is directed at releasing a therapeutic agent to the bloodstream from a polyurethane stent coating. However, polyurethane coatings have shown significant biocompatability problems. Artherosclerotic plaques, which obstruct blood vessels, are treated by balloon angioplasty and placement of stents at the obstruction site. However, the aftermath of angioplasty is often problematic as the blood vessel can re-close and a clot can form. Furthermore, other plaques can become unstable and rupture causing myocardial infarction and strokes. Wound repair of the blood vessel after balloon catheter dilation and stent placement involves proliferation of medical smooth muscle cells, migration of cells to the intima, and growth of intimal smooth muscle cells to form a thickened neointima. When a stent is placed at the site, the neointima grows over the stent. In about 30% of patients, this tissue remodeling process produces restenosis (*i.e.*, narrowing) of the vessel, and a recurrence of related symptoms. Evidence suggests that MMPs contribute to the development of atherosclerotic plaques and post-angioplasty restenotic plaques. Celentano *et al.*, *J. Clin. Pharmacol.*, 37:991-1000 (1997).

Increased numbers of mast cells, T-lymphocytes, and macrophages have been found at the shoulder region of plaques. These cells have been implicated in the MMP activation cascade, and MMPs have been further linked to plaque

instability. Rupture or degranulation of mast cells during balloon angioplasty or stent placement releases tryptase and chymase which in turn activate MMPs.

Placement of a stent in a lumen can initiate a foreign body response. Macrophages have been shown to produce MMP-9, and activated macrophages secrete cytokines and growth factors, which in turn induce neighboring cells to produce MMPs.

Catheters of stents with attachments for administering a therapeutic agent have been described in U.S. patent Nos. 4,824,436 to Wolinsky, 4,832,688 to Sagae *et al.*, and 5,254,089 to Wang. Stents having a medicament-containing portion have been described in U.S. Patents No 5,419,760 to Narciso, Jr., and 5,439,446 to Barry. U.S. Patent No. 5,616,608 to Kinsella *et al.* describes a method of treating patients at risk of developing vascular disease with an antimicrotuble agent such as Taxol® (paclitaxel), or a water soluble taxol derivative. U.S. Patent No. 5,304,121 to Sahatjian describes a vascular catheter and balloon catheter for delivering an aqueous-mobile drug, where a portion of the exterior surface of the expandable balloon has a drug-impregnated hydrogel. U.S. Patent 5,716,981 to Hunter *et al.* describes a drug eluting stent coated with an anti-angiogenic composition having a polymeric carrier. U.S. Patent No. 5,591,227 to Dinh *et al.* describes a drug eluting stent coated with a solid composite of a polymer and a therapeutic substance in an adherent layer, and fibrin in an adherent layer of the composite.

U.S. Patent No. 5,773,428 to Castelhano *et al.* and U.S. Patent No. 5,773,438 to Levy *et al.* describe certain chemical agents which have MMP-inhibiting properties. U.S. Patent No. 5,698,515 to Plate *et al.* describes certain insulin-containing polymer compositions.

Surgical procedures performed in the peritoneal cavity lead to the formation of adhesions. Adhesions are characterized by the formation of a fibrin

matrix during regrowth of epithelial cells due to injuries. It is believed that new epithelial cell growth attachment is regulated by MMPs. Additionally, most gynecologic surgical procedures result in the formation of adhesions.

It is believed that MMPs also play a significant role in many pathological conditions including cancer, heart disease, and wound healing. In disease states, an increase in MMP activity is observed, resulting in detrimental effects due to the increased degradation of ECM components.

Loss of articular cartilage is the most important pathological lesion occurring in equine articular disorders such as osteoarthritis. MMP-2 and MMP-9 have been implicated in this degradation of articular cartilage matrix.

It is thus desirable to reduce or inhibiting the effects or activity of MMPs in a patient suffering from a variety of diseases, conditions, and disorders.

Summary of the Invention

It has now been found that certain polymers and polymer compositions are effective inhibitors of MMPs.

In its broadest sense, the invention relates to polymeric compositions and devices having these polymeric compositions for reducing or inhibiting the undesired effects or activity of MMPs. This includes situations where (i) the unwanted or elevated MMP activity as a cause of the disorder or disease, (ii) the MMP is part of an observable manifestation of the disease or disorder, or (iii) the unwanted or elevated MMP activity is part of a biochemical or cellular cascade that results in or relates to the disease or disorder.

The invention thus relates to polymeric compositions and devices having a coating of these polymeric compositions for reducing or inhibiting the undesired effects or activity of MMPs, and methods therefor. The polymeric compositions may further contain one or more pharmaceutical agents. The

pharmaceutical agents may themselves have MMP-inhibiting activity. Specific diseases, conditions, and disorders caused or affected by unwanted MMP activity are described herein.

Suitable devices include stents, catheters, guidewires, aortic shunts, dialysis grafts, implants, or similar devices having a polymeric coating capable of inhibiting or countering the activity or effects of MMPs in the body.

In one embodiment, the invention relates to a drug eluting stent having a generally tubular structure coated with an MMP-inhibiting polymeric composition. The polymeric composition is capable of inhibiting or reducing the activity of MMPs. The stent can be a vascular, biliary, urethral, esophageal, or tracheal/bronchial stent for expanding the lumen passageway. In a preferred embodiment, the invention relates to a method for expanding the lumen passageway in a patient by inserting a coated stent according to the invention into a passageway to treat or eliminate vascular, biliary, urethral, esophageal, or tracheal/bronchial obstruction.

Filed concurrently with this application are U.S. Application Serial Nos. _____, _____, and _____. These applications describe novel stents, stent configurations, and stent sensors. The contents of these applications are hereby incorporated by reference.

The invention further relates to methods for treating or preventing blood vessel disease through the administration of an MMP-inhibiting polymer composition. Types of blood vessel disease include restenosis (*i.e.*, narrowing of blood vessels), aortic aneurysm, and unstable atherosclerotic plaques (including those which form following angioplasty). The invention further relates to use of a catheter, or implantation of a stent using the MMP-inhibiting compositions alone or in conjunction with stent, catheter, guidewire, or similar device.

The compositions can further be administered to reduce or inhibit undesired surgical adhesion (*i.e.*, scarring), inflammatory response, and neointimal thickening, as well as arthritis, and inflammatory joint diseases.

A variety of ulcerated conditions also can be treating in accordance with the invention, including those in the cornea as a result of alkali burns, or those resulting from infection by Pseudomonas aeruginosa, Acanthamoeba, Herpes simplex and vaccinia viruses.

Additional MMP-related conditions include periodontal disease, epidermolysis bullosa, and scleritis.

The invention further relates to the treatment of tumors in a patient through the administration of an MMP-inhibiting polymer. Such tumors include colorectal, cervical, lung, breast, bladder, prostate, skin cancers, and brain tumors.

It will be appreciated that the invention further relates to the use of polymers which have biologically specific sites bound to them. This includes polymers with an MMP inhibitor bound to the polymer chain. The inhibitor is itself specific to a certain MMP or groups of MMPs, and is capable of extracting or binding-up that MMP from the environment (*i.e.*, site in the body). This includes MMP and TIMP inhibitors that have been suitably modified to be covalently bound to the polymer.

Brief Description of the Drawings

Figure 1 is an enlarged side view of a MMP-inhibiting polymeric coating of the invention on an intralumenal stent.

Figure 2 is an enlarged view of the MMP-inhibiting coating displaced on a filament of a medical device such as a stent.

Detailed Description of the Invention

The invention thus relates to polymeric compositions and devices having these compositions for reducing or inhibiting the undesired effects or activity of MMPs.

In a preferred embodiment, the invention relates to a method of reducing or inhibiting the effects or activity of matrix metalloproteinases by administering to a patient an effective amount of a matrix metalloproteinase inhibiting polymer composition according to the invention.

In another preferred embodiment, the invention relates to a hydrophilic polymer coating for a medical device, where the coating includes a polymer composition according to the invention capable of inhibiting the action of matrix metalloproteinases in the body. Suitable medical devices include stents, catheters, guidewires, and implants. The coating may further contain one or pharmaceutical agents.

In one aspect, the invention relates to a method for delivery of a matrix metalloproteinase inhibiting substance to the interior of a body lumen having the steps of (i) providing a generally cylindrical stent body having a surface, (ii) providing a coating on the surface of the stent body, the coating having at least one matrix metalloproteinase inhibiting polymer, (iii) introducing the stent transluminally into a selected portion of the body lumen, and (iv) radially expanding the stent into contact with the body lumen.

Referring to Figure 1, a preferred stent **1** consists of a filamental braided design, having filaments **2**. The filaments **2** have a metal core, and an MMP-inhibiting coating **3**. The coating **3** is shown on a portion of a filament **2**, but it will be appreciated that the coating **3** can be applied to some or all of the

filaments **2** of the stent **1**. This coating can further contain one or more pharmaceutical agents.

Referring to Figure 2, the MMP-inhibiting coating **3** is displaced on the filament **2** of a medical device such as a stent.

The invention further relates to a method of treating blood vessel disease through the administration of an effective amount of a matrix metalloproteinase inhibiting polymer composition of the invention to a patient. Blood vessel diseases include artherosclerosis, restenosis, and aortic aneurysm.

In another embodiment, the invention also relates to compositions and methods of treating the undesired effects of angiogenesis in the body. This includes compositions and methods of treating various cancers, such as angiosarcoma, Kaposi's sarcoma, glioblastoma multiforme, hemangio blastoma (including Hippel-Lindan disease and hemangio pericytoma), basal cell carcinoma, and various tumor cell metastases. Undesired angiogenesis has also been implicated in neovascularization of the eye which can cause blindness. Inhibition of angiogenesis can also be useful in treating proliferative diabetic retinopathy, and neovascular glaucoma, as well as immune system conditions such as rheumatoid arthritis, angiolymphoid hyperplasia with eosinophilia; and skin conditions such as cavernous hemangioma (including Kasabach-Merritt syndrome) and psoriasis.

The compositions and methods of the invention can be further used to treat a variety of disorders and diseases including skin inflammations, superficial wounds, epidermolysis bullosa, pemphigus, paraplegia, chronic renal failure, Cushings disease, keratomalacia, scleromalacia perforans, septic shock, adult respiratory distress syndrome (ARDS).

Because the remodeling of bone involves MMPs, the compounds of the invention are useful in preventing or decreasing prosthesis loosening.

The methods and compounds of the invention can be used to inhibit MMPs which destroy structural proteins, interfere with inter- and intracellular signaling, including those implicated in cytokine up-regulation, or cytokine processing, or inflammation, and tissue degradation.

The invention also relates to a method of treating or preventing surgical adhesions through the administration to a patient of an effective amount of a matrix metalloproteinase inhibiting polymer composition of the invention.

The invention also relates to a method of treating connective tissue disease by administering to a patient an effective amount of a matrix metalloproteinase inhibiting polymer composition of the invention. Connective tissue diseases include arthritis, osteoarthritis, and endometriosis.

Generally speaking, preferred polymers are those that have the ability to chelate zinc or calcium, or both, as well as those having the ability control the oxidation cycle necessary to activate MMPs. Polymers with sulfide side groups are also suitable. Cross-linked polymers are preferred.

Most preferred matrix metalloproteinase inhibiting polymers are anionic polymers, preferably anionic hydrogels. Hydrogels are polymers that swell in water. As used herein, "Swelling" refers to the taking up of a liquid by a gel with an increase in volume. Only those liquids that solvate a gel can cause swelling. The swelling of protein gels is influenced by pH and the presence of electrolytes. Hydrogels have a large molecular weight that generally cannot be measured by conventional methods because it is too large, and are composed of a polymer backbone and crosslinks. The crosslinks can be used to extend the molecular weight of a polymer if the ratio of crosslinker to non-crosslinker is low, and polymerization is confined below the gel point. Nevertheless, if the ratio of

crosslinking monomer to none crosslinker is high enough, a gel is formed that while still being able to swell in a solvent, it does not truly dissolve. Preferred anionic hydrogels include sulfonated anionic hydrogels and carboxylic acid anionic hydrogels. Preferred sulfonated anionic hydrogels include AMPS, SEM (sulfoethylmethacrylate), SPM (sulfopropyl methacrylate), SPA (sulfopropyl acrylate), N,N-dimethyl-N-methacryloxyethyl-N-(3-sulfopropyl)ammonium betaine, methacryllic acid amidopropyl-dimethyl ammonium sulfobetaine, and SPI {itaconic acid-bis(1-propyl sulfonizacid-3) ester di-potassium salt}. These may be in the form of sulfonated monomers or polymers. Preferred carboxylic acid anionic hydrogels are acrylic acids, methacrylic acids, itaconic acids, AMBC, beta-carboxyethyl acrylate (acrylic acid dimers), maleic anhydride-methylvinyl ether polymers, and EDTA modified natural polymers.

Suitable polymers also include Carbopol® type polymers. Carbomer resins are high molecular weight, allylpentaerythritol-crosslinked, acrylic acid-based polymers, modified with C_{10}-C_{30} alkyl acrylates. A number of agencies, including the USP-NF, and United States Adopted Names Council (USAN) have adopted the generic name "carbomer" for the Carbopol family of resins. There are many carbomer resins available, with viscosity ranges from 0-80,000 cps.

These polymers can be cross-linked with polyalkenyl ethers or divinyl glycol. When in the presence of water or other suitable solvents (ethanol, methanol, etc.) these polymers form hydrogels. U.S. Patent Nos. 4,267,103, 5,349,030, 4,996,274, 4,509,949, 5,373,044 describe these polyacrylic acid polymers, including Carbopol®. The entire contents of these patents are incorporated herein by reference.

The polymers for use in the invention may be homopolymers, copolymers, and block copolymers, including diblock, triblock, multiblock, graft, or starblock copolymers.

Polymers with enhanced metal chelation or with reactive sulfhydryl groups or bound inhibitors directed against MMPs thus have enhanced activity against MMPs and can also be designed and optimized to fit specific desired applications. Polymers which are capable of chelating divalent metals such as zinc, calcium, and the like are thus preferred.

It has now been found that the recited polymers are effective MMP-inhibiting agents, and are thus useful as coatings for medical devices placed in the body, for example on stents, catheters, guidewires, and implants. The coating provides the MMP inhibition necessary to decreases local excess MMP breakdown of ECM in the arteries, thereby preventing or treating cardiac problems such as restenosis, myocardial infarction (MI) or unstable angina. The invention thus relates to the use of polymeric components as matrix metalloproteinase inhibitors specifically directed at prevention of restenosis and unstable Atherosclerotic plaque after angioplasty or implantation of a stent.

Another aspect of the invention involves monitoring the appearance, buildup and reduction of different MMP's during the injury and healing phase of stent insertion and healing. Webb *et al.* studied the relationship of MMPs to TIMP-1 following balloon catheter angioplasty in rat carotid arteries. Webb *et al.*, *Arter. Thromb. & Vasc. Biol.*, 17:1837-1844 (1997). It has been found that some MMP's, such as MMP-2, appear but are not associated directly with the healing process. Other MMPs, such as MMP-3 or MMP-9, appear to peak and are markers for trauma in the vessel wall. A release profile matched for specific MMP's is thus advantageous to aid in promoting safe healing following stent insertion. In particular, if one MMP's appearance or concentration profile signals restenosis, shutting down part of the cascade of MMP's can significantly impact the level of restenosis.

In another embodiment, therefore, the invention relates to the controlled release of agents in the recited polymer and polymer compositions to inhibit key

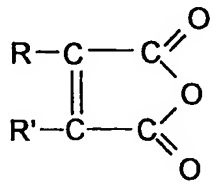
steps in the MMP cascade. This serves to head off the MMP overproduction leading to restenosis.

As noted, suitable polymers in accordance with the invention include homopolymers of unsaturated polymerizable carboxylic acids. This includes acrylic acids, methacrylic acids, maleic acids, maleic anhydrides, itaconic acids and the like; or copolymers of said acid or anhydride monomers with (meth)acrylate esters, (meth)acrylamides, olefins, maleic anhydrides, vinyl esters, vinyl ethers, and styrenics; or copolymers with other vinyl or vinylidene monomers. Copolymers of these acids may be cross-linked with small amounts of crosslinking agents. These materials are normally prepared by polymerization with a free radical catalyst in an organic medium in a closed vessel or autoclave equipped with stirring. During polymerization, the polymer precipitates from the solution as it is formed. The precipitated polymer is recovered and dried to remove residual solvent. The polymer in a powder form is used by dispersing it in water and neutralizing it to use its thickening, suspending or emulsifying ability. Such polymers are disclosed in U.S. Pat. Nos. 2,798,053; 3,915,921; 3,940,351; 4,062,817; 4,066,583; and 4,267,103.

Typical materials are those described in U.S. Pat. No. 2,798,053. Copolymers, for example, include copolymers of acrylic acid with small amounts of polyalkenyl polyether cross-linkers that are gel-like polymers, which, especially in the form of their salts, absorb large quantities of water or solvents with subsequent substantial increase in volume. Other useful carboxyl-containing polymers are described in U.S. Pat. No. 3,940,351, directed to polymers of unsaturated carboxylic acid and at least one alkyl acrylic or methacrylic ester where the alkyl group contains 10 to 30 carbon atoms, and U.S. Pat. Nos. 5,034,486; 5,034,487; and 5,034,488; which are directed to maleic anhydride copolymers with vinyl ethers. Other types of such copolymers are described in U.S. Pat. No. 4,062,817 where the polymers described in U.S. Pat. No. 3,940,351 contain another alkyl acrylic or methacrylic ester and the

alkyl groups contain 1 to 8 carbon atoms. Carboxylic polymers and copolymers such as those of acrylic acid and meth-acrylic acid also may be cross-linked with polyfunctional materials as divinyl benzene, unsaturated diesters and the like, as is disclosed in U.S. Pat. Nos. 2,340,110; 2,340,111; and 2,533,635. The disclosures of all of these U.S. patents are hereby incorporated herein by reference.

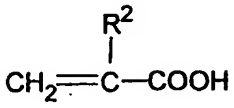
The carboxylic monomers are olefinically-unsaturated carboxylic acids containing at least one activated carbon-to-carbon olefinic double bond, and at least one carboxyl group; that is, an acid or function readily converted to an acid containing an olefinic double bond which readily functions in polymerization because of its presence in the monomer molecule, either in the alpha-beta position with respect to a carboxyl group, -C=C-COOH; or as part of a terminal methylene grouping, CH_2=C. Olefinically-unsaturated acids of this class include such materials as the acrylic acids typified by the acrylic acid itself, alpha-cyano acrylic acid, beta methylacrylic acid (crotonic acid), alpha-phenyl acrylic acid, beta-acryloxy propionic acid, cinnamic acid, p-chloro cinnamic acid, 1-carboxy-4-phenyl butadiene-1,3 itaconic acid, citraconic acid, mesaconic acid, glutaconic acid, aconitiic acid, maleic acid, fumaric acid, and tricarboxy ethylene. As used herein, the term "carboxylic acid" includes polycarboxylic acids and acid anhydrides, such as maleic anhydride, wherein the anhydride group is formed by the elimination of one molecule of water from two carboxyl groups located on the same carboxylic acid molecule. Maleic anhydride and other acid anhydrides useful herein have the general structure:



wherein R and R' are selected from the group consisting of hydrogen, halogen, and cyano (-C=N) groups, and alkyl, aryl, alkaryl, aralkyl, and cycloalkyl

groups such as methyl, ethyl, propyl, octyl, decyl, phenyl, tolyl, xylyl, benzyl, cyclohexyl, and the like.

Preferred carboxylic monomers are mono-olefinic acrylic acids having the general structure:



wherein R^2 is selected from the class consisting of hydrogen, halogen, and cyano (C=N) groups, monovalent alkyl radicals, monovalent aryl radicals, monovalent aralkyl radicals, monovalent alkaryl radicals and monovalent cycloaliphatic radicals. Of this class, acrylic and methacrylic acid are most preferred. Other useful carboxylic monomers are maleic acid and its anhydrides.

The polymers also may be cross-linked with a polyene, *e.g.*, decadiene or trivinyl cyclohexane; acrylamindes, such as methylene bis acrylamide; polyfunctional acrylates, such as trimethylol propane triacrylate; or polyfunctional vinylidene monomer containing at least 2 terminal CH_2 groups, including for example, butadiene, isoprene, divinyl benzene, divinyl naphthlene, allyl acrylates and the like. Particularly useful cross-linking monomers for use in preparing the copolymers are polyalkenyl polyethers having more than one alkenyl ether grouping per molecule. The most useful possess alkenyl groups in which an olefinic double bond is present attached to a terminal methylene grouping, CH_2=C. They are made by the etherification of a polyhydric alcohol containing at least 2 carbon atoms and at least 2 hydroxyl groups. Compounds of this class may be produced by reacting an alkenyl halide, such as allyl chloride or allyl bromide, with a strongly alkaline aqueous solution of one or more polyhydric alcohols. The product may be a complex mixture of polyethers with varying numbers of ether groups. Efficiency of the polyether cross-linking agent increases with the number of potentially polymerizable groups on the

molecule. It is preferred to utilize polyethers containing an average of two or more alkenyl ether groupings per molecule. Other cross-linking monomers include for example, diallyl esters, dimethallyl ethers, allyl or methallyl acrylates and acrylamides, tetraallyl tin, tetravinyl silane, polyalkenyl methanes, diacrylates, and dimethacrylates, divinyl compounds such as divinyl benzene, polyallyl phosphate, diallyloxy compounds and phosphite esters and the like. Typical agents are allyl pentaerythritol, allyl sucrose, trimethylolpropane triacrylate, 1,6-hexanediol diacrylate, trimethylolpropane diallyl ether, pentaerythritol, triacrylate, tetramethylene dimethacrylate, ethylene diacrylate, ethylene dimethacrylate, triethylene glycol dimethacrylate, and the like. Allyl pentaerythritol, trimethylolpropane diallylether and allyl sucrose provide excellent polymers. When the cross-linking agent is present, the polymeric mixtures usually contain up to about 5% or more by weight of cross-linking monomer based on the total of carboxylic acid monomer, plus other monomers, if present, and more preferably about 0.01 to 3.0 weight percent.

Other vinylidene monomers may also be used, including the acrylic nitriles. The useful α, β-olefinically unsaturated nitriles are preferably the mono-olefinically unsaturated nitriles having from 3 to 10 carbon atoms such as acrylonitrile, methacrylonitrile, and the like. Most preferred are acrylonitrile and methacrylonitrile. The amounts used are, for example, for some polymers are from about 1 to 30 weight percent of the total monomers copolymerized. Acrylic amides containing from 3 to 35 carbon atoms including monoolefinically unsaturated amides also may be used. Representative amides include acrylamide, methacrylamide, N-*t*-butyl acrylamide, N-cyclohexyl acrylamide, higher alkyl amides, where the alkyl group on the nitrogen contains from 8 to 32 carbon atoms, acrylic amides including N-alkylol amides of alpha, beta-olefinically unsaturated carboxylic acids including those having from 4 to 10 carbon atoms such as N-methylol acrylamide, N-propanol acrylamide, N-methylol methacrylamide, N-methylol maleimide, N-methylol maleamic acid

esters, N-methylol-p-vinyl benzamide, and the like. Still further useful materials are alphaolefins containing from 2 to 18 carbon atoms, more preferably from 2 to 8 carbon atoms; dienes containing atom 4 to 10 carbon atoms; vinyl esters and allyl esters such as vinyl acetate; vinyl aromatics such as styrene, methyl styrene and chlorostyrene; vinyl and allyl ethers and ketones such as vinyl methyl ether and methyl vinyl ketone; chloroacrylates; cyanoaklkyl acrylates such as α-cyanomethyl acrylate, and the α-, β-, and γ-cyanopropyl acrylates; alkoxyacrylates such as methoxy ethyl acrylate; haloacrylates as chloroethyl acrylate; vinyl halides and vinyl chloride, vinylidene chloride and the like; divinyls, diacrylates and other polyfunctional monomers such as divinyl ether, diethylene glycol diacrylate, ethylene glycol dimethacrylate, methylene-bis-acrylamide, allylpentaerythritol, and the like; and bis (β-haloalkyl) alkenyl phosphonates such as bis (β-chloroethyl) vinyl phosphonate and the like as are known to those skilled in the art. Copolymers wherein the carboxy containing monomer is a minor constituent, and the other vinylidene monomers present as major components are readily prepared in accordance with the process of this invention.

Steric stabilizers function to provide a steric barrier which repulses approaching particles. A requirement for the steric stabilizer is that a segment of the dispersant (*i.e.*, a hydrophobe) be very soluble in the solvent (the continuous phase in a nonaqueous dispersion polymerization process) and that another segment (*i.e.*, a hydrophile) be at least strongly adhered to the growing polymer particle. Thus, the steric stabilizers have a hydrophilic group and a hydrophobic group. The steric stabilizers are block copolymers having a soluble block and an anchor block having a molecular weight (*i.e.*, chain length) usually well above 1000, but a hydrophobe length of more than 50 Angstroms (Å), as calculated by the Law of Cosines. These dimensions are determined on the extended configuration using literature values for bond lengths and angles. Thus the steric stabilizers of the present invention are distinguishable from the prior art

steric surfactants which may be block copolymers, but have hydrophobe lengths of less than 50 Angstroms. The steric stabilizer of the present invention has either a linear block or a comb configuration, and has a hydrophobe of sufficient length to provide a sufficient steric barrier.

When the steric stabilizer is a linear block copolymeric steric stabilizer, it is defined by the following formula:

$$C_w\text{-}(\text{-B-A-B}_y)_x\text{-}D_z$$

where A is a hydrophilic moiety, having a solubility in water at 25°C of 1% or greater, a molecular weight of from about 200 to about 50,000, and selected to be covalently bonded to the B blocks; B is a hydrophobic moiety, having a molecular weight of from about 300 to about 60,000, a solubility of less than 1% in water at 25°C., capable of being covalently bonded to the A blocks; C and D are terminating groups which can be A or B; can be the same or different groups, and will depend upon the manufacturing process since they are present to control the polymer length, to add other functionality, or as a result of the manufacturing process; w is 0 or 1; x is an integer of 1 or more, y is 0 or 1, and z is 0 or 1.

Examples of such hydrophilic groups are polyethylene oxide, poly(1,3-dioxolane), copolymers of polyethylene oxide or poly (1,3-dioxolane), poly(2-methyl-2-oxazoline polyglycidyl trimethyl ammonium chloride, polymethylene oxide, and the like, with polyethylene oxide being preferred. Examples of hydrophobic groups are polyesters, such as those derived from 2-hydroxybutyric acid, 3-hydroxybutyric acid, 4-hydroxybutyric acid, 2-hydroxycaprioc acid, 10-hydroxydecanoic acid, 12-hydroxydodecanoic acid, 16-hydroxyhexadecanoic acid, 2-hydroxyisobutyric acid, 2-(4-hydroxyphenoxy) propionic acid, 4-hydroxyphenylpyruvic acid, 12-hydroxysteraric acid, 2-hydroxyvaleric acid, polylactones, such as caprolactone, butyrolactone, polylactams, such as those derived from caprolactam, polyurethanes, polyisobutylene, where the

hydrophobe should provide a steric barrier of greater than 75 Angstroms, with greater than 100 Angstroms being also preferred, and the like, with polyhydroxy fatty acids, such as poly(12-hydroxystearic acid) being preferred. The steric barrier is the length of the hydrophobe in its fully-extended condition. Such steric stabilizers are commercially available under the brand name Hypermer® from Imperial Chemical Industries, Inc.

In accordance with the invention, the hydrophilic coating also serves to give a lubricious surface with little friction during movement. Additionally, the bioadhesive properties of the polymers help to hold a temporary catheter in place. Thus, an active coating for temporary medical devices may also benefit from a coating that combines these features. Carbopol®-type polymers are suitable for this application. While certain polyacrylic acids are currently used in the art as a lubricious (*i.e.*, lubricating) coating on catheters and guidewires as a coating, they are not used as bioadhesives.

In another aspect, the invention relates to a hydrophilic, lubricious polymer coating for a medical device wherein the polymer coating is capable of holding a beneficial therapeutic agent at the site or release therapeutic agents to the site.

It has now been found that the MMP-inhibiting polymers of the invention are also useful in wound healing. Because the bioadhesive qualities of these polymers causes retention on damaged tissue, the combination of MMP inhibition and bioadhesion allows these polymers to play a functional role in normal wound repair.

There is increasing evidence to indicate that individual MMPs have an important role in tumor spread and invasion. The presence of MMP-2, MMP-2,

and MMP-9 in esophageal cancer was recently observed. Murray *et al., J. Pathol.*, 185(3): 256-61 (1998).

In the treatment of malignant tumors, the most common reason for treatment failure is metastases. The heterogeneity of size, age, anatomical location, and biologic composition of these metastases makes effective surgical, radiologic and chemotherapy therapy difficult. It has now been found that tumors can be treated through the MMP-inhibiting polymers of the invention. The treatment of tumors can be achieved by placing at least one MMP-inhibiting polymer in the proximity of known or excised tumors. The bioadhesive and MMP inhibiting qualities of the polymers are effective at limiting tumor progression. Ability to flow and cover irregular cavities after tumor excision would also be beneficial to the activity of this polymer. Polymers with relatively low rates of clearance from the site are preferred.

The MMP-inhibiting polymers are also suitable for the treatment of adhesions formed as a result of surgical procedures, including adhesions in the peritoneal cavity, and adhesions resulting from gynecologic surgical procedures. The invention also relates to a barrier polymer that promotes wound healing and helps to regulate the MMP activity may reduce the formation of adhesions. Preferred polymers include polyacrylic acid (PAA) hydrogel polymers capable of bioadhesion without the need for sutures or other fixation mechanisms.

In endometriosis, a similar disease state, incorrect levels of TIMP-1 may be related to increased degradation of ECM components of the peritoneal cavity and contribute to endometriosis. TIMP-1 levels in conjunction with MMP-1 and MMP-9 are believed to be involved.

The invention thus further relates to a polymer system that can be applied in the peritoneal cavity, thereby regulating the activity of these enzymes, and reducing the spread of this disease state.

Foreign body response mediated by macrophages may also be related to MMP activity. For example, macrophages secrete MMP-9 (gelatinase B). The polymers of the invention and coatings thereof when applied to a device help to control the macrophage response, reduce inflammatory response, and lead to acceptance of the device in the body.

The invention further relates to the treatment of human and equine osteoarthritis through local or systemic administration of an effective MMP-inhibiting polymer.

Polymers of the invention that have activity in a broad spectrum against MMP may be used as actives or functional adjuncts in a multitude of pharmaceutical applications.

Peptidyl thiols incorporating a carbonyl group two atoms removed from the thiol group have been shown to be potent MMP inhibitors. See U.S. Patent No. 5,852,213. This includes compounds where the thiol is further distant from an amide carbonyl and mercaptoalcohols which have the stereo specific conformation.

Active stereospecific thiol compounds may be bound to the present polymers via disulfide bonds. A polymer with thiol side groups can be used to deliver these active thiol containing therapeutics. The thiol therapeutic and polymer may be oxidized to form a disulfide link. This may then be reduced via reaction with the body such as the thioredoxin system, glutathione, and other sulfide reducing systems of the body. Such linking methods are known. See for

example *J. Med. Chem.*, 36:4030 (1993); U.S. Patent Nos. 5,852,213 and 4,595,700; as well as WO/9407481; WO/9513289; and WO/9509833.

To reversibly bind a thiol-containing compound to a carboxyllic acid functional polymer, one method that can be used is to form a thiol ester bond. This is achieved by converting a portion of the carboxylic acid side groups to acyl halides using techniques known in the art. The polymer-containing acyl halide will then react with thiol-containing compounds to form the thiol ester. The thiol ester group can then undergo hydrolysis to regenerate the thiol containing compound and the carboxylic acid functionalized polymer.

U.S. Patent No. 5,849,951 describes typical hydroxamic acid inhibitor synthesis using solid support. The functional groups in the polystyrene solid support, for example, can be incorporated as a small co-monomer amount in the instant polymers. The contents of this patent are hereby incorporated by reference.

Polymers which present hydroxyl groups as the points of attachment for the compound may be used as derivatives of benzyl alcohol, the peptide, or non- peptide being attached as a benzyl ester and cleaved by hydrolysis, acidolysis or aminolysis to release the compound as a carboxylic acid, or as a carboxamide. Also suitable are polymer substrates which present amino groups, including derivatives of piphenylmethylamine, the peptide or non-peptide being attached as a carboxamide and cleaved by acidolysis to release the peptide or non peptide as a carboxamide. Substitution of such linkers by a nitro group enables the photolytic cleavage of the peptide or non peptide from the residue of the solid substrate.

The polymers in accordance with the invention may be bound to an active compound which is directly or indirectly linked to the relevant N or O atom by a covalent bond which is cleavable by acid hydrolysis. Within carboxylic acid polymers, a small amount of the amine substituted monomer or hydroxyl substituted monomer can be copolymerized or generated through methods

known in the art of solid phase peptide synthesis. Known base substrates also include amino- and hydroxy- functionalized solid substrates, *i.e.*, those which are chemically modified by introduction of amino or hydroxyl groups, to serve as convenient points for further chemical manipulation.

It is known in the art of solid phase peptide synthesis that hydroxyl- or amino-carrying linker groups can be introduced onto amino and hydroxy functionalized solid substrates, the linker group having characteristics which facilitate the cleavage of the desired synthesized molecule from the solid support. Thus, for hydroxyl-carrying linker groups, the first amino acid of the peptide to be constructed can be attached as an ester formed between the linker-presented hydroxyl group and the carboxyl group of the amino acid. For amino-carrying linker groups, the first amino acid of the peptide can be attached as a carboxamide formed between the linker-presented amino group and the carboxyl group of the amino acid. An example of a solid support resin presenting amino groups on linker groups attached to the base substrate is the resin 5-(4'-aminomethyl-3',5'-dimethoxyphenoxy)-(N,4-methylbenzhydryl)-pentyramide copolymer. Protecting groups can be employed during the synthesis to protect hydroxyl groups, amine groups carboxyl protecting group. However, the product containing the protecting groups can be further treated, in one or several steps, before or after isolation from the reaction medium, to remove any amine protecting group, carboxyl protecting group or hydroxyl protecting group present. Removal of amine protecting groups, carboxyl protecting groups or hydroxyl protecting groups are known. T. W. Greene, *Protective Groups in Organic Synthesis*, 2nd Edition, (New York, 1991). Active compounds of the hydroxamic acid family can also be bound to the polymer through an hydroxamate ester. Through hydrogenation, the hydroxamic acid is liberated from the polymers. Reaction of a polymer containing styrene with CH_2Cl side group is then converted to an O-benzyl hydroylamine side group through known techniques. This functional precursor is then bound to a stereospecific carboxylic acid, or ester or acyl chloride through conventional

peptide coupling conditions to link the stereospecific hydroxamate to the polymeric support. Through hydrolysis reactions in the body, the free hydroxamic acid is generated. Compounds and active inhibitors in this regards are described in *e.g.*, U.S. Patent Nos. 5,830,915; 5,773,428; 5,872,152; 5,849,951; 5,840,939; 5,763,621; 5,747,514; 5,700,838; 5,691,382; and 5,652,262. The contents of these patents are hereby incorporated by reference.

Photoaging of undamaged skin due to UVB irradiation exposure is inhibited by administering an agent that inhibits the activity of UVB irradiation inducible MMPs in the skin. In skin care, MMPs are implicated in the remodeling or "turnover" of skin. As a result, the regulation of MMPs can improve the treatment of skin conditions including, wrinkle repair, regulation and prevention and repair of ultraviolet induced skin damage. Such treatments includes prophylactic treatment or treatment before the physiological manifestations are apparent. For example, the MMP inhibitor can be applied as a pre-exposure treatment to prevent ultraviolet damage during or after exposure to prevent or minimize post-exposure damage. In addition, MMPs have been implicated in skin disorders and diseases related to abnormal tissues that result from abnormal turnover, which includes metalloprotease activity, such as epidermolysis bullosa, psoriasis, scleroderma and atopic dermatitis. The compounds and compositions of the invention are also useful for treating the consequences of "normal" injury to the skin including scarring or "contraction" of tissue, for example, following burns. MMP inhibition is also useful in surgical procedures involving the skin for prevention of scarring, and promotion of normal tissue growth including in such applications as limb reattachment and refractory surgery (whether by laser or incision). For example, they are thought to be useful in treating or preventing viral infection, including infection which would result in herpes, "cold" (*e.g.*, rhinoviral infection).

Because MMPs are implicated in the inflammatory response, and in the processing of cytokines the compounds are also useful as anti-inflammatories,

the compounds and compositions are useful in treating diseases where inflammation is prevalent including, inflammatory bowel disease, Crohn's disease, ulcerative colitis, diverticulitis, and Reiter's Syndrome.

It will be appreciated that the compositions according to the invention may further include one or more pharmaceutical agents. Suitable pharmaceutical agent categories include glucocorticoids, dexamethasone, dexamethasone sodium phosphate, isothiozolones, anticoagulants, heparin, hirudin, peptides, oligopeptides, angiopeptin, antimitotic agents, polynucleotides, and oligonucleotides, sulfyhdryls, and hydroxamic acids.

A preferred group of pharmaceutical agents are MMP-inhibitors. Preferred MMP inhibitors include phosphinic acid amides such as those described in U.S. Patent No. 5,830,915 to Pikul *et al.* Also preferred MMP-inhibiting pharmaceutical agents include hydroxyamide MMP-inhibitors described in U.S. Patent No. 5,696,147 to Galardy *et al.* The disclosure of these patents is hereby incorporated by reference.

For example, N-acetyl cystine (NAC) is a peptide involved in the inhibition or deactivation of MMPs, and is suitable for use in the invention. It is believed that redox stress modulates cellular MMP expression; thus anti-oxidants in coatings may not only reduce the oxidative degradation of the polymer, but may also reduce production of MMPs involved in stimulating remodeling. Other anti-oxidants such as Vitamin E and probucol may have more than one pathway of benefit in co-formulation in stent coatings and stent coatings with these ingredients would be beneficial.

Especially preferred MMP inhibiting agents include cyclopentanecarboxylic acid {2-(4'-chloro-1,1'-biphenyl-4-yl) carbonyl-5-(phenylthio), (1-alpha, 2-beta, 5-beta)}; arylsulfonylamino hydroxamic acid derivatives such as 2-(R)-2(2-benzylcarbamoylmethyl)-(4-methoxybenzenesulfonyl)amino-N-hydroxy-3-methylbutyr-amide; arylsulfonyl hydrox-amic acid derivatives; substituted 4-arylbutyric acid derivatives such as

4-(4-(3-phenoxyprop-1-ynyl)phenyl)-4-oxo-2-(2-phthalimidoethyl) butyric acid; bis-sulfonamides hydroxamic acids; thiophenebutanoic acid derivatives; mercaptoketones and mercaptoalcohols.

It will be appreciated that compounds which bind zinc at the active site of the enzyme prevent the catalytic activity of MMPs and are especially preferred. MMP inhibitor activity has been found in certain peptidyl hydroxamic acids, peptidylalkyl carboxylic acids, peptidylphosphinic and phosphonic acids. Furthermore, peptidyl thiols incorporating a carbonyl group two atoms removed from the thiol group have been shown to be potent MMP inhibitors.

Additional preferred MMP inhibiting agents include hydroxamic acids; macrocyclic amino carboxylates; isothiazolones; 2,5-Diarylisothiazolone; phosphinamide-based hydroxamic acids; caprolactam succinate; achiral drugs; malonyl alpha-mercaptoketones and alpha-mercaptoalcohols; diketopiperazine; succinamide hydroxamate (alpha gem-disubstituted succinamide methyl/allyl substitution); hydroxamic acids such as those disclosed in *J. Med. Chem.* 1998 15:41 (2) 199-223 (two key hydrogen bonds must be present here between the enzyme and potent substrates; potent inhibitors possess strong zinc-binding functionalities); hydroxamic acids with Ireland-Claisen rearrangements (alpha-cyclopentyl group); succinyl mer-captoalcohol and mercaptoketones such as succinyl mercaptoketones and diastereomeric mercaptoalcohols; diazepine-based hydroxamic acids; hydroxamates (benzylic ethers with a 4- or 5- carbon CH_2 linker; phenylglycine; peptide inhibitors such as Ac-RCGVPD-NH_2; Ac-RCGVP-NH_2; and Ac-isoCGY-(2,6 dichlorobenzyl)-P-NH2; carboxyalkyl peptides such as those having biphenylylethyl groups and halogenated biphenylylethyls, including 2(R)-[2-(4'-fluro-4-biphenylyl)ethyl]-4(S)-n-butyl-1,5-pentane dioic acid 1-(alpha(S)-tert-butylglycine methylamide) amide; thiadiazole (including 5-substituted-1,3,4-thiadiazole-2-thiones); thiols; thiophenes such as batimastat; malonic acids such as (2R,S)-HONH-CO-CH(i-Bu)-CO-Ala-Gly-NH_2; non-peptidic cysteine derivatives such as L-cysteine, N- and C-terminal

derivatizations, N-benzyloxycarbonyl-L-cysteine-(2-phenyl)ethylamides; and N-sulfonylamino acids such as aryl sulfonamides, biaryl, tetrazoles, amides, and triple bond-carrying variants.

Additional preferred MMP inhibiting agents include cyclic sulfone derivatives such as those described in U.S. Patent No. 5,883,131 to Pfizer, substituted cyclo-alkanecarboxylic acid derivatives as matrix metalloprotease inhibitors such as those described in U.S. Patent No. 5,874,473 to Bayer Corporation.

A number of additional pharmaceutical agents can be used in accordance with the invention. Suitable types of pharmaceutical agents include, for example, polynucleotides, oligonucleotides, peptides (such as oligopeptides and polypeptides) including cytokines, proteins, enzymes, hormones, monoclonal antibodies, human growth hormones, clotting factors, colony stimulating factors, erythropoietins, tissue plasminogen activators, recombinant soluble receptors, and vaccines.

Preferred pharmaceutical agents include cytokines, antibacterial agents, anti-neoplastic agents, anti-fungal agents, immunomodulators, antiparasitic agents, and CNS agents. Preferred pharmaceutical agents thus include taxane-related antineoplastic agents such as paclitaxel (Taxol®), anthracyclines (including doxorubicin, daunorubicin, epirubicin, idarubicin, mithoxanthrone and carminomycin), mitomycin-type antibiotics, polyene antifungals such as amphotericin B, immunomodulators including tumor necrosis factor alpha (TNFα), and interferons.

Suitable preferred agents include antibacterial agents such as penicillin-related compounds including 9-lactam antibiotics, broad spectrum penicillins, and penicillinase-resistant penicillins (such as ampicillin, ampicillin-sublactam, nafcillin, amoxicillin, cloxacillin, methicillin, oxacillin, dicloxacillin, azocillin, bacampicillin, cyclacillin, carbenicillin, carbenicillin indanyl, mezlocillin, penicillin G, penicillin V, ticarcillin, piperacillin, aztreonam and imipenem, cephalosporins

(cephalosporins include first generation cephalosporins such as cephapirin, cefaxolin, cephalexin, cephradine and cefadroxil; second generation cephalosporins such as cefamandole, cefoxitin, cefaclor, cefuroxime, cefuroxime axetil, cefonicid, cefotetan and ceforanide; third generation cephalosporins such as cefotaxime, ceftizoxime, ceftriaxone, cefoperazone and ceftazidime), tetracyclines (such as demeclocytetracycline, doxycycline, methacycline, minocycline and oxytetracycline), beta-lactamase inhibitors (such as clavulanic acid), aminoglycosides (such as amikacin, gentamicin C, kanamycin A, neomycin B, netilmicin, streptomycin and tobramycin), chloramphenicol, erythromycin, clindamycin, spectinomycin, vancomycin, bacitracin, isoniazid, rifampin, ethambutol, aminosalicylic acid, pyrazinamide, ethionamide, cycloserine, dapsone, sulfoxone sodium, clofazimine, sulfonamides (such as sulfanilamide, sulfamethoxazole, sulfacetamide, sulfadiazine, and sulfisoxazole), trimethoprim-sulfamethoxazole, quinolones (such as nalidixic acid, cinoxacin, norfloxacin and ciprofloxacin), methenamine, nitrofurantoin and phenazopyridine. Such agents further include agents active against protozoal infections such as chloroquine, diloxanide furoate, emetine or dehydroemetine, 8-hydroxyquinolines, metronidazole, quinacrine, melarsoprol, nifurtimox, pentamidine, sodium stibogluconate and suramin.

Suitable pharmaceutical agents also include antifungal agents such as amphotericin-B, flucytosine, ketoconazole, miconazole, itraconazole, griseofulvin, clotrimazole, econazole, terconazole, butoconazole, ciclopirox olamine, haloprogin, toinaftate, naftifine, nystatin, natamycin, undecylenic acid, benzoic acid, salicylic acid, propionic acid and caprylic acid. Suitable agents further include antiviral agents such as zidovudine, acyclovir, ganciclovir, vidarabine, idoxuridine, trifluridine, foxcarnet, amantadine, rimantadine, and ribavirin.

The polymer compositions can further comprise a variety of polypeptides including antibodies, immunomodulators or cytokines (including interferons or

interleukins), peptide hormones (such as colony stimulating factors and tumor necrosis factors), hormone receptors, neuropeptides, lipoproteins (such as α-lipoprotein), erythropoietins, growth hormones, thyroid hormones, toxins such as diphtheria toxin, proteoglycans such as hyaluronic acid, and glycoproteins such as gonadotropin hormone.

The polymers also can be administered in conjunction with enzyme inhibiting agents such as reverse transcriptase inhibitors, protease inhibitors, angiotensin converting enzymes, 5α-reductase, and the like. Typical agents include peptide and nonpeptide agents including finasteride, lisinopril, saquinavir, quinapril, ramipril, indinavir, ritonavir, nelfinavir, zalcitabine, zidovudine, allophenylnorstatine, kynostatin, delaviridine, *bis*-tetrahydrofuran ligands, and didanosine.

It will be appreciated that combinations of these agents can also be employed. It will be further appreciated that the invention is not directed to the underlying specific activity of these agents, but rather to the compositions themselves.

Chemotherapeutic agents appropriate for use in the invention also include, vinca alkaloids (such as vincristine and vinblastine), mitomycin-type antibiotics (such as mitomycin-C and N-methyl mitomycin-C), bleomycin-type antibiotics such as bleomycin A2, antifolates such as methotrexate, aminopterin, and dideaza-tetrahydrofolic acid, colchicine, demecoline, etoposide, taxanes such as paclitaxel (Taxol®), and anthracycline antibiotics. Suitable tetracycline antibiotics include, without limitation, doxorubicin, daunorubicin, carminomycin, epirubicin, idarubicin, mithoxanthrone, 4-demethoxy-daunomycin, 11-deoxydaunorubicin, 13-deoxydaunorubicin, adriamycin-14-benzoate, adriamycin-14-octanoate, or adriamycin-14-naphthaleneacetate.

The appropriate dosage for the pharmaceutical agents will often be about comparable to that of the pharmaceutical agent alone; dosages will be set by the prescribing medical professional considering many factors including age, weight,

and condition of the patient, as well as the pharmacokinetics of the specific agent. Often the amount of agent required for effective treatment will be less than the amount required using the free pharmaceutical agent. Generally, an effective amount of pharmaceutical agents is that amount effective to reduce the symptoms of the disease sought to be treated, or to induce a pharmacological change relevant to treating the disease sought to be treated.

The foregoing detailed description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom. Hence, numerous modifications and changes can be made by those skilled in the art without departing from the spirit and scope of the invention.

The following examples will serve to further typify the nature of the invention but should not be construed as a limitation on the scope thereof, which is defined solely by the appended claims.

EXAMPLE 1

For a stent made of Nitinol (an alloy of Nickel and Titanium), the surface of this type of stent material is primarily titanium oxide. A coating of polyacrylic acid or similar hydrophilic material is applied to a stent by the following methods.

A thin layer (or "tie layer") is placed directly on the stent. The tie layer adheres tightly to the metal oxide surface and provides a layer that is easily activated to bind the hydrophilic polymer. In adhering the hydrophilic portion to the tie layer, the tie layer is preferably extremely smooth. Blood compatible polymer is used, and a solvent coated on the stent. An aprotic solution of a polyacrylic acid solution is then contacted with the stent giving a smooth layer of bound hydrophilic polymer and reacting out residuals. Tricoates of an amine polymer, an anionic polymer and amine polymer have also been used to give a reactive surface to bind hydrophilic groups.

Alternatively, to attach the hydrophilic coating the surface of the metal stent is activated to produce sites where free radical polymerization or

attachment may occur. Epoxide grafting, aldehyde grafting, and other activation sequences can alternatively be used to bind the hydrophilic polymer to the tie layer. Sterilization of the coating through high temperature treatment or epoxide treatment may be used to further bind or crosslink hydrophilic coatings.

Therapeutic agents can be placed into the hydrogel coating so that their release is slow as they exit the tortuous polymer network. Therapeutic agents that have low solubility are loaded in this manner so that both their solubility and the pathway from the gel control release.

Therapeutic agents can be permanently bound to the hydrogel coating so that they are held in close proximity to the stent. These therapeutic agents can be agents that protect the blood vessel immediately surrounding the stent from neointima proliferation. Preferred therapeutic agents are those that work on one of the factors in a cascade of sequences leading to medical complications such as clots, myocardial infarction (MI) or unstable angina as well. In this instance, the constant presence of the therapeutic agent at the site reduces the body's inflammatory and thrombotic response to the stent. These agents do not need to enter the cells to be effective such that these therapeutic agents work on factors found in the blood. Heparins can be end-bound to the matrix to decrease clotting. NAC and other MMP-inhibiting sulfhydryl compounds can be bound to the polymer.

Therapeutic agents can also be reversibly bound to the hydrogel coating so that their release is slower than that seen with therapeutic agents entrapped in the hydrogel. Reversible linkages such as a hydrolyzable esters, amides, disulfides, and extended peptide links are suitable.

The hydrogel coating does not have to be the same on both sides of the stent. There can be a combination of materials that is more beneficial to the luminal side that is different from the combination on the wall side. Both sides of the device do not have to be coated inside or outside, coating may be deemed enough for the application based on *in vivo* results.

EXAMPLE 2

Preparation of Aqueous Dispersions of Carbopols®

Carbomer preparations are primarily used in aqueous systems, although other liquids can be used. In water, a single particle of carbomer will wet very rapidly but, like many other powders, tend to form clumps of particles when haphazardly dispersed in polar solvents. As the surfaces of these clumps solvate, a layer is formed which prevents rapid wetting of the interior of the clumps. When this occurs, the slow diffusion of solvent through this solvated layer determines the mixing or hydration time. To achieve fastest dispersion of the carbomer, it is added very slowly into the vortex of the liquid as it is stirred very rapidly. Almost any device, like a simple sieve, that can sprinkle the powder on the rapidly stirred liquid is useful.

A neutralizer is added to thicken the gel after the carbomer is dispersed. Sodium hydroxide or potassium hydroxide can be used in carbomer dispersions containing less than 20% alcohol. Triethanolamine will neutralize carbomer resins containing up to 50% ethanol. Other neutralizer agents include sodium carbonate, ammonia and borax.

Air bubbles incorporated into the gel are removed prior to adding the neutralizing agent. Air bubbles are removed using an ultrasonic unit or by allowing the product to stand.

Carboxymethylcellulose in concentrations of 4-6% of the medium viscosity grades can be used to produce gels; glycerin may be added to prevent drying. Precipitation can occur at pH values less than 2; it is most stable at pH levels between 2 and 10, with maximum stability at pH 7 to 9. It is incompatible with ethanol.

What is Claimed

1. A method for delivery of a matrix metalloproteinase inhibiting substance to the interior of a body lumen comprising the steps of:
providing a generally cylindrical stent body having a surface;
providing a coating on the surface of the stent body comprising at least one matrix metalloproteinase inhibiting polymer;
introducing the stent transluminally into a selected portion of the body lumen; and
radially expanding the stent into contact with the body lumen.

2. The method according to claim 1 wherein the matrix metalloproteinase inhibiting polymer is an anionic polymer.

3. The method according to claim 2 wherein the anionic polymer is an anionic hydrogel.

4. The method according to claim 3 wherein the anionic hydrogel is selected from the group consisting of sulfonated anionic hydrogels, and carboxylic acid anionic hydrogels.

5. The method according to claim 4 wherein the sulfonated anionic hydrogel is selected from the group consisting of AMPS, sulfoethylmethacrylate (SEM), sulfopropyl methacrylate (SPM), sulfopropyl acrylate (SPA), N,N-dimethyl-N-methacryloxyethyl-N-(3-sulfopropyl)-ammonium betaine, methacrylic acid amidopropyl-dimethyl ammonium sulfobetaine, and SPI {itaconic acid-bis(1-propyl sulfonizacid-3) ester di-potassium salt}.

6. The method according to claim 4 wherein the carboxylic acid anionic hydrogel is selected from the group consisting of acrylic acids, methacrylic acids, itaconic acids, beta-carboxyethyl acrylate, AMBC, maleic anhydride-methylvinyl ether polymers, and EDTA modified natural polymers.

7. The method according to claim 1 wherein the coating further comprises at least one pharmaceutical agent.

8. The method according to claim 7 wherein the pharmaceutical agent is selected from the group consisting of glucocorticoids, dexamethasone, dexamethasone sodium phosphate, isothiozolones, anticoagulants, heparin, hirudin, peptides, oligopeptides, angiopeptin, antimitotic agents, polynucleotides, oligonucleotides, sulfyhdryls, hydroxamic acids, mercaptoketones, and mercaptoalcohols.

9. A hydrophilic polymer coating for a medical device comprising a polymer composition capable of inhibiting the action of matrix metalloproteinases in the body.

10. The coating according to claim 9 wherein the matrix metalloproteinase inhibiting polymer composition comprises an anionic polymer.

11. The coating according to claim 10 wherein the anionic polymer is an anionic hydrogel.

12. The coating according to claim 11 wherein the anionic hydrogel is selected from the group consisting of sulfonated anionic hydrogels, and carboxylic acid anionic hydrogels.

13. The coating according to claim 12 wherein the sulfonated anionic hydrogel is selected from the group consisting of AMPS, sulfoethylmethacrylate (SEM), sulfopropyl methacrylate (SPM), sulfopropyl acrylate (SPA), N,N-dimethyl-N-methacryloxyethyl-N-(3-sulfopropyl)-ammonium betaine, methacrylic acid amidopropyl-dimethyl ammonium sulfobetaine, and SPI {itaconic acid-bis(1-propyl sulfonizacid-3) ester di-potassium salt}.

14. The coating according to claim 12 wherein the carboxylic acid anionic hydrogel is selected from the group consisting of acrylic acids, methacrylic

acids, itaconic acids, beta-carboxyethyl acrylate, AMBC, maleic anhydride-methylvinyl ether polymers, and EDTA modified natural polymers.

15. The coating according to claim 9 wherein the coating further comprises at least one pharmaceutical agent.

16. The coating according to claim 15 wherein the pharmaceutical agent is selected from the group consisting of glucocorticoids, dexamethasone, dexamethasone sodium phosphate, isothiozolones, anticoagulants, heparin, hirudin, peptides, oligopeptides, angiopeptin, antimitotic agents, polynucleotides, oligonucleotides, sulfyhdryls, hydroxamic acids, mercaptoketones, and mercaptoalcohols.

17. The coating according to claim 9 wherein the medical device is selected from the group consisting of stents, catheters, guidewires, and implants.

18. A method of reducing or inhibiting the effects or activity of matrix metallo-proteinases comprising administering to a patient an effective amount of a matrix metalloproteinase inhibiting polymer composition.

19. The method according to claim 18 wherein the matrix metalloproteinase inhibiting polymer composition comprises an anionic polymer.

20. The method according to claim 19 wherein the anionic polymer is an anionic hydrogel.

21. The method according to claim 20 wherein the anionic hydrogel is selected from the group consisting of sulfonated anionic hydrogels, and carboxylic acid anionic hydrogels.

22. The method according to claim 21 wherein the sulfonated anionic hydrogel is selected from the group consisting of AMPS, sulfoethylmethacrylate (SEM), sulfopropyl methacrylate (SPM), sulfopropyl acrylate (SPA), N,N-dimethyl-N-methacryloxyethyl-N-(3-sulfopropyl)-ammonium betaine,

methacrylic acid amidopropyl-dimethyl ammonium sulfobetaine, and SPI {itaconic acid-bis(1-propyl sulfonizacid-3) ester di-potassium salt}.

23. The method according to claim 21 wherein the carboxylic acid anionic hydrogel is selected from the group consisting of acrylic acids, methacrylic acids, itaconic acids, beta-carboxyethyl acrylate, AMBC, maleic anhydride-methylvinyl ether polymers, and EDTA modified natural polymers.

24. The method according to claim 18 wherein the polymer composition further comprises at least one pharmaceutical agent.

25. The method according to claim 24 wherein the pharmaceutical agent is selected from the group consisting of glucocorticoids, dexamethasone, dexamethasone sodium phosphate, isothiozolones, anticoagulants, heparin, hirudin, peptides, oligopeptides, angiopeptin, antimitotic agents, polynucleotides, oligonucleotides, sulfyhdryls, hydroxamic acids, mercaptoketones, and mercaptoalcohols.

26. A method of treating blood vessel disease comprising administering to a patient a matrix metalloproteinase inhibiting amount of a polymer composition.

27. The method according to claim 26 wherein the matrix metalloproteinase inhibiting polymer composition comprises an anionic polymer.

28. The method according to claim 27 wherein the anionic polymer is an anionic hydrogel.

29. The method according to claim 28 wherein the anionic hydrogel is selected from the group consisting of sulfonated anionic hydrogels, and carboxylic acid anionic hydrogels.

30. The method according to claim 29 wherein the sulfonated anionic hydrogel is selected from the group consisting of AMPS, sulfoethylmethacrylate

(SEM), sulfopropyl methacrylate (SPM), sulfopropyl acrylate (SPA), N,N-dimethyl-N-methacryloxyethyl-N-(3-sulfopropyl)-ammonium betaine, methacrylic acid amidopropyl-dimethyl ammonium sulfobetaine, and SPI {itaconic acid-bis(1-propyl sulfonizacid-3) ester di-potassium salt}.

31. The method according to claim 29 wherein the carboxylic acid anionic hydrogel is selected from the group consisting of acrylic acids, methacrylic acids, itaconic acids, beta-carboxyethyl acrylate, AMBC, maleic anhydride-methylvinyl ether polymers, and EDTA modified natural polymers.

32. The method according to claim 26 wherein the blood vessel disease is a disease selected from the group consisting of artherosclerosis, restenosis, and aortic aneurysm.

33. The method according to claim 26 wherein the polymer composition further comprises at least one pharmaceutical agent.

34. The method according to claim 33 wherein the pharmaceutical agent is selected from the group consisting of glucocorticoids, dexamethasone, dexamethasone sodium phosphate, isothiozolones, anticoagulants, heparin, hirudin, peptides, oligopeptides, angiopeptin, antimitotic agents, polynucleotides, oligonucleotides, sulfyhdryls, hydroxamic acids, mercaptoketones, and mercaptoalcohols.

35. A method of treating cancer comprising administering to a patient a matrix metalloproteinase inhibiting amount of a polymer composition.

36. The method according to claim 35 wherein the matrix metalloproteinase inhibiting polymer composition comprises an anionic polymer.

37. The method according to claim 36 wherein the anionic polymer is an anionic hydrogel.

38. The method according to claim 37 wherein the anionic hydrogel is selected from the group consisting of sulfonated anionic hydrogels, and carboxylic acid anionic hydrogels.

39. The method according to claim 38 wherein the sulfonated anionic hydrogel is selected from the group consisting of AMPS, sulfoethylmethacrylate (SEM), sulfopropyl methacrylate (SPM), sulfopropyl acrylate (SPA), N,N-dimethyl-N-methacryloxyethyl-N-(3-sulfopropyl)-ammonium betaine, methacrylic acid amidopropyl-dimethyl ammonium sulfobetaine, and SPI {itaconic acid-bis(1-propyl sulfonizacid-3) ester di-potassium salt}.

40. The method according to claim 38 wherein the carboxylic acid anionic hydrogel is selected from the group consisting of acrylic acids, methacrylic acids, itaconic acids, beta-carboxyethyl acrylate, AMBC, maleic anhydride-methylvinyl ether polymers, and EDTA modified natural polymers.

41. The method according to claim 35 wherein the polymer composition further comprises at least one pharmaceutical agent.

42. The method according to claim 41 wherein the pharmaceutical agent is selected from the group consisting of glucocorticoids, dexamethasone, dexamethasone sodium phosphate, isothiozolones, anticoagulants, heparin, hirudin, peptides, oligopeptides, angiopeptin, antimitotic agents, polynucleotides, oligonucleotides, sulfyhdryls, hydroxamic acids, mercaptoketones, and mercaptoalcohols.

43. A method of treating or preventing surgical adhesions comprising administering to a patient an effective amount of a matrix metalloproteinase inhibiting polymer composition.

44. The method according to claim 43 wherein the matrix metalloproteinase inhibiting polymer composition comprises an anionic polymer.

45. The method according to claim 44 wherein the anionic polymer is an anionic hydrogel.

46. The method according to claim 45 wherein the anionic hydrogel is selected from the group consisting of sulfonated anionic hydrogels and carboxylic acid anionic hydrogels.

47. The method according to claim 46 wherein the sulfonated anionic hydrogel is selected from the group consisting of AMPS, sulfoethylmethacrylate (SEM), sulfopropyl methacrylate (SPM), sulfopropyl acrylate (SPA), N,N-dimethyl-N-methacryloxyethyl-N-(3-sulfopropyl)-ammonium betaine, methacrylic acid amidopropyl-dimethyl ammonium sulfobetaine, and SPI {itaconic acid-bis(1-propyl sulfonizacid-3) ester di-potassium salt}.

48. The method according to claim 46 wherein the carboxylic acid anionic hydrogel is selected from the group consisting of acrylic acids, methacrylic acids, itaconic acids, beta-carboxyethyl acrylate, AMBC, maleic anhydride-methylvinyl ether polymers, and EDTA modified natural polymers.

49. The method according to claim 43 wherein the polymer composition further comprises at least one pharmaceutical agent.

50. The method according to claim 49 wherein the pharmaceutical agent is selected from the group consisting of glucocorticoids, dexamethasone, dexamethasone sodium phosphate, isothiozolones, anticoagulants, heparin, hirudin, peptides, oligopeptides, angiopeptin, antimitotic agents, polynucleotides, oligonucleotides, sulfyhdryls, hydroxamic acids, mercaptoketones, and mercaptoalcohols.

51. A method of treating connective tissue disease comprising administering to a patient an effective amount of a matrix metalloproteinase inhibiting polymer composition.

52. The method according to claim 51 wherein the matrix metalloproteinase inhibiting polymer composition comprises an anionic polymer.

53. The method according to claim 52 wherein the anionic polymer is an anionic hydrogel.

54. The method according to claim 53 wherein the anionic hydrogel is selected from the group consisting of sulfonated anionic hydrogels and carboxylic acid anionic hydrogels.

55. The method according to claim 54 wherein the sulfonated anionic hydrogel is selected from the group consisting of AMPS, sulfoethylmethacrylate (SEM), sulfopropyl methacrylate (SPM), sulfopropyl acrylate (SPA), N,N-dimethyl-N-methacryloxyethyl-N-(3-sulfopropyl)-ammonium betaine, methacrylic acid amidopropyl-dimethyl ammonium sulfobetaine, and SPI {itaconic acid-bis(1-propyl sulfonizacid-3) ester di-potassium salt}.

56. The method according to claim 54 wherein the carboxylic acid anionic hydrogel is selected from the group consisting of acrylic acids, methacrylic acids, itaconic acids, beta-carboxyethyl acrylate, AMBC, maleic anhydride-methylvinyl ether polymers, and EDTA modified natural polymers.

57. The method according to claim 51 wherein the connective tissue disease is a disease selected from the group consisting of arthritis, osteoarthritis, and endometriosis.

58. The method according to claim 51 wherein the polymer composition further comprises at least one pharmaceutical agent.

59. The method according to claim 47 wherein the pharmaceutical agent is selected from the group consisting of glucocorticoids, dexamethasone, dexamethasone sodium phosphate, isothiozolones, anticoagulants, heparin, hirudin, peptides, oligopeptides, angiopeptin, antimitotic agents,

polynucleotides, oligonucleotides, sulfyhdryls, hydroxamic acids, mercaptoketones, and mercaptoalcohols.

Figure 1

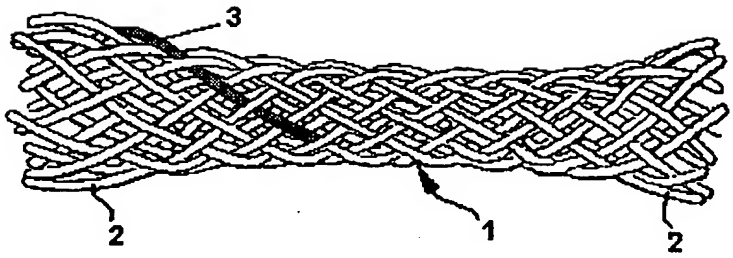


Figure 2

INTERNATIONAL SEARCH REPORT

Inte...ational Application No
PCT/US 00/07158

A. CLASSIFICATION F SUBJECT MATTER
IPC 7 A61K9/00 A61L31/00 A61P9/10 A61P35/00 A61P41/00 A61P19/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 197 13 213 A (RUEBBEN ALEXANDER DR MED) 1 October 1998 (1998-10-01) column 1, line 1 - line 60 column 3, line 25 -column 4, line 20; figures 3-5 claims	1-4, 6-12, 14-21, 23-29, 31-34
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2000	28/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

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INTERNATIONAL SEARCH REPORT

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PCT/US 00/07158

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